ALCOHOL CONSUMPTION AND BREAST CANCER IN THE EPIDEMIOLOGIC FOLLOW-UP STUDY OF THE FIRST NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY

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Abstract We investigated the relation between alcohol consumption and breast cancer in the Epidemiologic Follow-up Study of the first National Health and Nutrition Examination Survey, a cohort study based on a sample of the U.S. population. A total of 7188 women 25 to 74 years of age who were examined during the period 1971 through 1975 were included in the analysis. Information about alcohol consumption was obtained during the base-line interview. The median follow-up period for this cohort was 10 years. One hundred twenty-one cases of breast cancer that developed after the base-line examination were identified through hospital records or death certificates.

The relative-risk estimate for any amount of drinking relative to no drinking was 1.5 (95 percent confidence interval, 1.1 to 2.2). The estimates for three levels of consumption, from the lowest to the highest, were 1.4 (confidence interval, 0.9 to 2.3), 1.5 (0.9 to 2.6), and 1.6 (1.0 to 2.7), in comparison to no drinking at all. These relative-risk estimates were not materially affected by adjustment for known risk factors for breast cancer or for several dietary factors.

The results of this study, consistent with those of two other cohort studies and a number of case–control studies, suggest that moderate alcohol consumption is associated with an elevation in the risk of breast cancer of 50 to 100 percent. (N Engl J Med 1987; 316: 1169-73.)

SEVERAL epidemiologic studies have shown a relation between moderate drinking and breast cancer. Hiatt and Bawol reported a 40 percent excess risk of breast cancer in women who had three or more drinks per day in a cohort study based on the members of a prepaid group practice.[1] In a cohort study of U.S. nurses by Willett and coworkers, women who reported moderate alcohol consumption were approximately 50 percent more likely to go on to have breast cancer than those who drank little or no alcohol.[2] Although some case–control studies have not found an association between alcohol consumption and breast cancer,[3-7] others have detected an increased risk with moderate drinking.[8-15]

We report here the results of an investigation of the relation of moderate alcohol consumption and breast cancer incidence in a cohort study based on a sample of the U.S. population.

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METHODS

The NHANES I Epidemiologic Follow-up Study (NHEFS) is a prospective cohort study generated from the original National Health and Nutrition Examination Survey (NHANES I).[16]

NHANES I was conducted by the National Center for Health Statistics from 1971 to 1975 in a sample of the civilian noninstitutionalized population of the United States.[17] Persons estimated to be at high risk for malnutrition (children, the elderly, women of childbearing age, and the poor) were oversampled to improve estimates of nutritional status for those groups. NHANES I included a sociodemographic and medical history, a standardized medical examination, a dietary questionnaire, hematologic and biochemical tests, and anthropometry.

Subjects were traced and interviewed again for the NHEFS between 1981 and 1984. A total of 14,407 adults 25 through 74 years of age who were examined during the period 1971 through 1975 were eligible for inclusion in the NHEFS. Of the 8596 women in this cohort, 83 percent were white.

A total of 131 cases of breast cancer were identified through hospital records or death certificates or both. For the 111 cases identified through hospital records, the date of the first admission

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for which breast cancer was listed as the discharge diagnosis was considered the incidence date. The date of death was regarded as the incidence date in the 20 cases for which only death-certificate data were available.

Women were excluded from the analytic cohort for the following reasons: base-line information on drinking was missing for 30 women; 281 women who were pregnant or breast-feeding at the time of the NHANES I interview were excluded, on the grounds that reported alcohol consumption might have been affected by these conditions (this included one case who was pregnant at base line); 675 of the eligible women could not be traced; 483 women were found to be alive but did not have a follow-up interview, because they either refused or could not be contacted; and 12 women with a history of breast cancer on the first hospital record were excluded as representing prevalent cases. A small number of women fell into more than one of these exclusion categories.

The analytic cohort consisted of 7188 women, including 121 with breast cancer. The median follow-up period for the cohort was 10 years.

At the base-line interview, each woman was asked whether she had had at least one drink of beer, wine, or liquor during the previous year. If she had, she was asked how often she drank (every day, just about every day, about 2 or 3 times a week, about 1 to 4 times a month, more than 3 but less than 12 times a year, or no more than 2 or 3 times a year). Women who reported having had at least one drink during the past year were also asked how much they usually drank in 24 hours (in glasses or drinks). The average daily number of ounces of ethanol consumed was calculated by multiplying (number of drinks per day) × (a factor reflecting frequency of drinking) × (0.5), with 0.5 oz being an estimate of the amount of ethanol in a shot of liquor, a 5-oz glass of wine, or a 12-oz glass of beer. The frequency factor was 1 for drinking every day, 5/7 for just about every day, 5/14 for 2 to 3 times a week, 5/60 for 1 to 4 times a month, 15/730 for 3 to 12 times a year, and 5/730 for 2 to 3 times a year. The number of ounces of ethanol was converted into the number of grams, with 1 oz considered approximately equal to 25 g (or roughly two drinks). Information on the quantity of the specific type of alcoholic beverage consumed was not available. Questions about drinking at earlier ages were asked in the follow-up interview, but the number of women with breast cancer who provided this information was too small for stable analysis at this time.

Information about age, education, poverty-index ratio, body-mass index, parity, age at menarche, age at menopause, and diet was obtained at the base-line interview. The dietary data were derived from a 24-hour recall interview conducted by a trained nutritionist using graduated three-dimensional models of food portions.[18] Standard food-composition data were used to calculate the intake of nutrients.[19] Information about any family history of breast cancer (in the subject's mother or sister) and the age at first parturition was available only from the follow-up interview. Information about smoking was collected at base line on only 43 percent of the women in the original NHEFS cohort. We inferred from the follow-up information the smoking status at base line of the women for whom such data were missing. The distributions of alcohol consumption and most breast cancer risk factors were virtually identical in the analytic and overall NHEFS cohorts. The analytic cohort was slightly older than the overall NHEFS cohort (26 vs. 23 percent ≥65 years) and had a slightly greater proportion of postmenopausal women (52 vs. 47 percent).

Crude incidence rates for a given category of drinking were calculated by dividing the number of cases of breast cancer occurring among women in the category by the total number of person-years contributed by the women in that category. The number of person-years contributed by an individual woman was calculated from base line to the time of breast cancer incidence, death, or the follow-up interview — whichever came first. In the light of the relatively small number of cases involved, age-adjusted rates were calculated by both the indirect and direct methods.[20]

We used Cox's proportional-hazards regression technique[21] to analyze the simultaneous relation of alcohol, age, and other variables to the incidence of breast cancer in the cohort. The analyses were performed with the PROC PHGLM procedure available in the SAS statistical package.[22]

Results

The mean age of the analytic cohort at base line was 49 years. Fifty-five percent of the women were under 50, and 25 percent were over 65. Forty-two percent had completed less than 12 years of education; 21 percent had completed some education beyond high school.

The relation of alcohol consumption to a number of previously suggested risk factors for breast cancer is shown in Table 1. Drinking was more frequent among women who were younger, women who had more education, those with a lower body-mass index, those with a later age at first parturition, those with lower parity, those who smoked, and those who ate more fat. There were negligible differences in the frequency of drinking in relation to menopausal status, family history of breast cancer, and age at menarche.

Table 1. Drinking in Relation to Other Risk Factors for Breast Cancer.

Risk Factor	Any Drinking (%)*
Age (yr)	
<50	59
50–64	47
≥65	29
Education (yr)	
<12	38
12	55
>12	64
Body-mass index (wt[kg]/ht[cm]^2)	
≤22.5	56
22.6–27.0	51
≥27.1	41
Age at first parturition	
<20	46
20–24	49
≥25	56
Parity	
0	55
1	51
2–3	52
≥4	42
Age at menarche	
<12	50
12–13	51
≥14	48
Menopausal status	
Premenopausal	49
Postmenopausal	49
Family history of breast cancer	
No	50
Yes	52
Total dietary fat (g/day)	
≤43.2	46
43.3–67.0	47
≥67.1	52
Smoking (pack-years)	
0	41
1–13	60
>13	64

*Each number represents the total amount of person-time accumulated by drinkers within a given risk-factor category as a percentage of the total amount of person-time accumulated by all subjects (drinkers plus nondrinkers) within that risk-factor category. All percentages, except those for age, have been age-adjusted by the direct method,[20] according to the distribution of age-specific person-times in the analytic cohort.

The incidence rate for breast cancer in this cohort was comparable to that observed in other U.S. populations, and the ratio of observed to expected cases (based on age-specific incidence rates from the Connecticut Cancer Registry) was 1.07 (95 percent confidence interval, 0.89 to 1.28). Women who had breast cancer were older than those who did not, with a mean base-line age of 56 for cases and 49 for non-cases.

Crude and age-adjusted incidence rates for breast cancer at the various levels of alcohol consumption are shown in Table 2. Age adjustment resulted in an increase in the difference in breast cancer rates between drinkers and nondrinkers.

Relative-risk estimates from proportional-hazards regression models that included variables for age and alcohol consumption are shown in Table 3. The relative-risk estimate for drinking as compared with not drinking was 1.5 (95 percent confidence interval, 1.1 to 2.2); the estimates for the three levels of drinking, from lowest to highest, were 1.4 (0.9 to 2.3), 1.5 (0.9 to 2.6), and 1.6 (1.0 to 2.7), respectively.

Analysis of various models that included variables for age, alcohol consumption, and one of several potential confounders yielded relative risks for the highest level of drinking in the range of 1.4 to 2.0; the potential confounders included were education (<12, 12, and >12 years), total dietary fat in grams per day (quintiles), age at first birth (<19, 19 through 20, 21 through 22, 23 through 25, and ≥26), age at onset of menarche (≤11, 12, 13, 14, and ≥15), parity (nulliparity, 1, 2, 3, and ≥4 live births), family history of breast cancer, menopausal status, body-mass index (quintiles), or cigarette smoking (never smoked, formerly smoked, currently smoking; or 0, 1 through 13, and >13 pack-years). Estimates did not change materially when quintile indicators for saturated fat or fat as a percentage of calories were substituted for total fat, nor were they altered in separate analyses that included quintile indicators for protein, dietary cholesterol, or total calories. Relative-risk estimates resulting from the simultaneous inclusion of a variety of potential confounders were 1.6 (confidence interval, 1.0 to 2.5) for any amount of drinking as compared with no drinking; for the three levels of drinking (relative to no drinking), the estimates from lowest to highest were 1.4 (0.8 to 2.5), 1.6 (0.9 to 3.1), and 2.0 (1.1 to 3.7) (Table 3).

Table 2. Crude and Age-Adjusted Breast Cancer Incidence Rates According to Level of Alcohol Consumption.

Alcohol Consumption	No. (Cases)	Crude Rate*	Age-Adjusted Rate*†
None	3646 (57)	166	154
Any (g/day)‡	3542 (64)	189	219
<1.3	1354 (25)	193	207
1.3–4.9	1158 (19)	170	222
≥5	1030 (20)	204	231

*Per 100,000 person-years.

†These rates have been age-adjusted by the indirect method,[20] on the basis of the crude and age-specific incidence rates for breast cancer among women 25 to 74 years of age from the Connecticut Cancer Registry. Age-adjusted rates calculated by the direct method[20] (on the basis of the age distribution of the analytic cohort) were 150 and 218, respectively, for no drinking and any drinking, and 206, 204, and 271 for the lowest through the highest levels of drinking.

‡Five grams of ethanol per day is roughly equivalent to three drinks per week.

Table 3. Relative-Risk Estimates for Breast Cancer According to the Level of Alcohol Intake.

Relative-Risk Estimate	Alcohol Intake Level (g/day)				
	None	Any	>0–1.2	1.3–4.9	≥5
Age-adjusted*	1.0	1.5	1.4	1.5	1.6
(95% confidence interval)		(1.1–2.2)	(0.9–2.3)	(0.9–2.6)	(1.0–2.7)
Multivariate†	1.0	1.6	1.4	1.6	2.0
(95% confidence interval)		(1.0–2.5)	(0.8–2.5)	(0.9–3.1)	(1.1–3.7)

*Based on age-adjusted regression coefficients from the proportional-hazards models (121 cases).

†Based on 88 cases with complete covariate information, including age (years); education (>12 years); body-mass index (combined second through fourth quintiles, 21 to 29; fifth quintile, ≥30); total dietary fat (grams per day) (separate second through fifth quintiles: 34.2 through 47.5; 47.6 through 61.4; 61.5 through 80.6; ≥80.7); age at first parturition (19 through 20, 21 through 22, 23 through 24, and ≥25), age at menarche (≤12), parity (nulliparity, 1 or 2 births), positive family history, and premenopausal status.

Multivariate proportional-hazards analysis (based on the model described in Table 3) of a linear-trend variable for alcohol consumption (with four values — no drinking and three levels of consumption) yielded a P value of 0.020 for that variable; similar analysis of a linear-trend variable confined only to the three drinking levels yielded a P value of 0.50.

To examine the possibility that the alcohol–breast cancer relation differed among risk-factor subgroups, we performed stratum-specific analyses for a number of risk factors (Table 4). The relative-risk estimate for any amount of drinking (relative to none) was highest in younger women, premenopausal women, and women with the lowest relative weight. No appreciable changes in the relative-risk estimates for drinking were observed in analyses carried out in the categories of age at first parturition, parity, age at menarche, family history of breast cancer, fat (number of grams per day or percentage of total calories), or smoking.

Discussion

In this cohort study of a probability sample of the U.S. population, consumption of any amount of alcohol conferred an increase in the risk of breast cancer of 50 to 100 percent. The data were compatible with a moderate dose–response relation at various levels of alcohol consumption. Our study showed a 40 to 50 percent increase in risk among the women who drank less than 5 g per day (equivalent to about three drinks per week), whereas the two previously reported cohort studies[1,2] demonstrated no increased risk at this low level of drinking. The discrepancy could reflect a generalized underreporting of alcohol consumption by women in the NHEFS cohort who drank, as compared with those who drank in the other two studies. Women in the NHEFS population did appear to be relatively light drinkers, with only 9 percent consuming one or

Table 4. Age-Adjusted Relative-Risk Estimates for Breast Cancer Associated with Any Drinking within Levels of Specific Risk Factors.

Risk Factor	No. of Cases	Relative-Risk Estimate (95% Confidence Interval)*
Age (yr)		
<50	46	2.1 (1.1–4.1)
50–64	21	1.6 (0.7–3.9)
≥65	54	1.2 (0.7–2.1)
Menopausal status		
Premenopausal	45	2.0 (1.0–3.8)
Postmenopausal	76	1.3 (0.8–2.1)
Body-mass index		
≤22.5	37	3.5 (1.6–7.9)
22.6–27.0	40	1.3 (0.7–2.5)
≥27.1	44	1.0 (0.5–1.9)

*Age-adjusted estimates computed from stratified proportional-hazards models that included age (in years). The reference category was nondrinking.

more drinks per day. The greatest risk in our study was seen among women who drank 5 g of alcohol or more per day. Willett et al. have calculated a relative risk of 1.3 for women consuming between 5.0 and 14.9 g per day, and of 1.6 for those consuming at least 15 g per day.[2] Hiatt and Bawol observed a relative risk of 1.4 that was restricted to women consuming three or more drinks per day.[1] It is noteworthy that elevated mortality rates from breast cancer have been observed in women with a history of heavy drinking.[23] Too few women reported heavy drinking in the NHEFS cohort for us to ascertain whether heavy drinking conferred an even greater excess risk.

Although our findings may reflect a true causal relation between alcohol and breast cancer, several alternative explanations need to be considered.

Our results would be biased if there were substantially more nondrinking or nearly nondrinking women with breast cancer in the group excluded from the analytic cohort than in that cohort itself. There is no reason to believe that the exclusion criteria used were related in this specific way both to alcohol consumption and breast-cancer status. Moreover, the similarity of risk-factor distributions in the analytic and overall NHEFS cohorts also argues against the presence of bias.

Since information on alcohol consumption was collected at base line in this prospective study, it is highly unlikely that women in whom breast cancer later developed systematically overestimated their drinking as compared with the women who did not acquire the disease.

Confounding by some factor associated with both alcohol consumption and breast cancer is another alternative to a causal explanation. Because older women, at greater risk of breast cancer, tended to drink less than younger women, adjustment for age resulted in a substantial increase in the relative-risk estimate. Control for other potential confounding variables, singly and in combination, had little effect on the age-adjusted estimates.

Confounding by dietary factors in particular has been proposed as an explanation for the association of alcohol with breast cancer. The inclusion of a number of dietary variables in the multivariate models actually resulted in a slight increase in the magnitude of that association. The assessment of a person's "usual" intake by the 24-hour-recall method, however, is limited by the substantial daily variation in nutrients consumed.[24] Although the 24-hour-recall method appears to yield reasonably accurate estimates of mean intake for population groups,[24] considerable misclassification can result when this method is used to assign individuals to groups according to levels of nutrient intake.[25] When the number of cases is relatively limited, as in this study, it is conceivable that misclassification on the basis of dietary exposure could result in inadequate control for confounding. We also cannot rule out the possibility that dietary patterns in early life were confounding the observed alcohol–breast cancer association.

No adequate history of benign breast disease was elicited in the NHEFS, either at base line or at follow-up. Although benign breast disease is associated with breast cancer, we are unaware of any studies showing a link between alcohol consumption and benign breast disease. Moreover, in the other two prospective studies of alcohol and breast cancer, in which information on benign breast disease was available, adjustment for this condition did not diminish the association of alcohol with breast cancer.[1,2] Confounding by a history of benign breast disease is therefore unlikely to account for our findings.

The association between drinking and breast cancer was stronger among younger as opposed to older women, leaner as opposed to heavier women, and premenopausal as opposed to postmenopausal women. For other risk factors, the relative-risk estimates were similar in all the subgroups. It is noteworthy that the risk of breast cancer associated with any amount of drinking was most elevated among the groups of women (younger and possibly leaner) with the lowest baseline risk. Alternatively, the increased risk among younger women may simply reflect the fact that drinking at earlier ages is hazardous, as Harvey et al. have recently suggested.[15] The apparent modification of effect at various levels of age, body-mass index, and menopausal status, however, needs to be interpreted cautiously, given the relatively small number of cases at each level.

Clinical and laboratory studies have suggested several mechanisms by which alcohol could exert a carcinogenic effect on breast tissue, including interference with hepatic metabolism and clearance,[26-28] stimulation of prolactin secretion,[29-31] alteration of cell membranes,[32,33] and circulation of cytotoxic protein products of ethanol metabolism.[34] In general, however, the proposed pathophysiologic mechanisms are still speculative.

Three cohort studies, conducted in different settings, have now shown an excess risk of breast cancer of approximately 50 percent associated with moderate alcohol consumption. Although it is difficult to exclude the possibility that unknown or poorly measured confounders are responsible for the elevated risks in this range, the consistency of these results is compelling. Moreover, given the frequency of breast cancer and the universality of drinking, even a small elevation in the relative risk of breast cancer would translate into considerable morbidity and mortality attributable to alcohol consumption.[35] Further epidemiologic studies of alcohol consumption and breast cancer, with particular attention to the type of alcohol consumed and the timing of drinking during a woman's life, are clearly indicated. Such studies should be complemented by additional laboratory investigations of the carcinogenic and transforming properties of "moderate" alcohol in animal models and cell-culture systems, as well as studies in humans of the effects of alcohol consumption on hormones and other pertinent biochemical factors.

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